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Note

Synthesis of some 3′-(5-substituted-3-mercapto-1,2,4-triazol-4-yl)spiro[indole-3,2′-thiazolidine]-2,4′-diones and 3-substituted-1,2,4-triazolo[3,4-*b*]indolo-[3,2-*e*][1,3,4]thiadiazoles as fungicides

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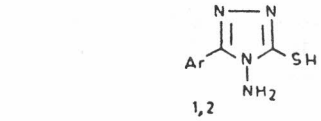
Synthesis of 3′-(5-substituted-3-mercapto-1,2,4-triazol-4-yl)spiro [indole-3,2′-thiazolidine]-2,4′-diones **5,7** has been achieved alongwith 3-substituted-1,2,4-triazolo[3,4-*b*]indolo[3,2-*e*][1,3,4]thiadiazoles **6,8** which have been assayed for their fungicidal activity.

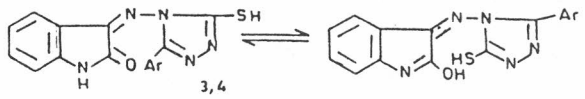
Indole nucleus plays an important role as a common denominator for various biocidal activities[1-5]. Likewise thiazolidinone derivatives are known to have antifungal, antibacterial, herbicidal and a host of other biological activities[6-8]. Several 1,2,4-triazoles have been patented as biocidal[9-11] agents. Reports pertaining to the pesticidal properties of thiadiazine ring are also available[12,13].

In continuation of our work on fused[14,15] and spiro heterocycles[16,17] of biocidal interest and guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably in comparison to the individual moieties, we synthesised the title compounds having 1,2,4-triazole, thiazolidinone or thiadiazine and indole as hterocyclic nuclei in a single molecule for the evaluation of their fungicidal activity. It is further interesting to note that the title compounds have some common structural features with the fungicidal spiro system[17] and spiro β-lactambarbiturate[18] which is a well known CNS drug.

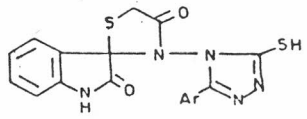
The required starting materials, 4-amino-5-aryl-3-mercapto-1,2,4-triazole **1** and 4-amino-5-aryloxymethyl-3-mercapto-1,2,4-triazole **2** were prepared according to the reported methods[19]. On condensation with isatin, **1** and **2** furnished



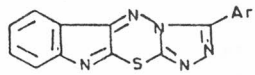
1,2



3,4



5,7



6,8

Ar = 

3a, R = H
3b, R = 2-Cl
3c, R = 2,4-Cl_2
3d, R = 2-Me
3e, R = 4-OMe
3f, R = 4-Cl

5a, R = H
5b, R = 2-Cl
5c, R = 2,4-Cl_2
5d, R = 2-Me
5e, R = 4-OMe

6a, R = 2-Me
6b, R = 4-Cl
6c, R = 2,4-Cl_2
6d, R = 4-OMe

Ar = CH_2O 

4a, R = H
4b, R = 4-Cl
4c, R = 4-Cl-3-Me
4d, R = 4-Me
4e, R = 2-Me
4f, R = 2-Cl

7a, R = H
7b, R = 4-Cl
7c, R = 4-Cl-3-Me
7d, R = 4-Me
7e, R = 2-Me

8a, R = H
8b, R = 2-Cl
8c, R = 2-Me
8d, R = 4-Me

respectively **3** and **4** which on treatment with mercaptoacetic acid produced the corresponding thiazolidinone derivatives **5** and **7**. Compounds **3** and **4** on cyclisation with conc. H_2SO_4 in cold afforded **6** and **8**, respectively.

Fungicidal Activity. The title compounds **5a-e**, **6a-d**, **7a-e** and **8a-d** were screened for their antifungal activity against *Pyricularia oryzae, Rhizoctonia solani, Pseudoperonospora cubensis* and *Phytophthora infestans* at 1000, 100 and 10 ppm concentrations, respectively. The results were compared with that of commercial fungicide carbendazim tested under similar conditions. Amongst these **5c**, **6b**, **6c** and **7b** showed activity nearly comparable (89-96% at 1000 ppm) to that of carbendazim (100% at 1000 ppm) (Table I).

Table I—Fungicidal activity of compounds **5a-e, 6a-d, 7a-e** and **8a-d** (mean % inhibition after 7 days)

Compd	*Pyricularia oryzae*		*Rhizoctonia solani*		*Pseudoperonospora cubensis*		*Phytophthora infestans*	
	1000 ppm	100 ppm	1000 ppm	100 ppm	1000 ppm	100 ppm	1000 ppm	100 ppm
5a	72	46	70	46	74	50	76	53
5b	76	48	77	52	74	54	74	53
5c	96	76	94	81	90	80	93	78
5d	70	41	68	45	69	46	74	49
5e	80	56	81	58	78	49	86	50
6a	58	43	65	44	61	38	65	43
6b	90	62	91	74	89	53	91	67
6c	90	60	91	74	89	53	90	63
6d	78	47	67	45	69	41	69	48
7a	65	51	65	39	69	53	70	46
7b	90	77	91	59	91	73	94	70
7c	80	57	82	51	83	56	78	56
7d	73	49	70	45	78	54	73	42
7e	67	37	66	39	72	51	68	38
8a	59	31	69	39	76	37	75	49
8b	79	54	74	48	76	44	79	55
8c	76	47	67	39	73	34	69	40
8d	70	50	71	46	78	57	70	52
Carben-dazim	100	97	100	94	100	96	100	95

Experimental Section

General — Melting points were taken in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer-881 spectrophotometer and ^{1}H NMR spectra on a Perkin-Elmer R-32 spectrometer at 60 MHz.

5-(2,4-Dichlorophenyl)-3-mercapto-4-[1′*H*-2′(3′*H*)-oxoindol-3′-ylimino]-1,2,4-triazole 3c. A mixture of 4-amino-5-(2,4-dichlorophenyl)-3-mercapto-1,2,4-triazole **1** (Ar = 2,4-Cl_2-phenyl) (2.61g, 0.01 mole) and isatin (1.47g, 0.01 mole) in methanol (30 mL) was refluxed for 3 hr. The solvent was removed and the residue poured into water. The solid compound, thus obtained, was filtered, washed, dried and recrystallised from aq. ethanol to get **3c**, mp 155 °C, yield 64%; IR(KBr): 3220, 2720, 1710, 1640, 1620, 1550, 1490, 1450, 1260 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.8-7.5 (m, 7H, Ar H), 8.5-8.8 (b, 1H, NH).

Likewise **3a** (182 °C, 73%), **3b** (150 °C, 76%), **3d**(121 °C, 81%) **3e** (141 °C, 79%) and **3f** (240, 63%) were prepared and also **4c** (mp 148 °C, yield 71%); IR(KBr): 3230, 2715, 1705, 1640, 1550, 1500, 1440 cm^{-1}; ^{1}H NMR(DMSO-d_6): δ 1.8 (s, 3H, CH_3) 4.2(d, 2H, OCH_2), 6.7-7.6 (m, 7H, Ar H), 8.4-8.8(b, 1H, NH). Analogously **4a**(108 °C, 70%), **4b**(122 °C, 69%) **4d**(104 °C, 71%), **4e**(170 °C, 70%) and **4f**(152 °C, 70%) were obtained.

3′-[5-(2,4-Dichlorophenyl)-3-mercapto- 1,2,4-triazol-4-yl]spiro [indole-3,2′-thiazolidine]-2,4′-dione 5c. A mixture of 5-(2,4-dichlorophenyl)-3-mercapto-4-[1′*H*-2′(3′*H*)-oxoindol- 3′-yl)imino]-1,2,4-triazole, **3c**(3.9g, 0.01 mole) and mercaptoacetic acid (1.0g, 0.011 mole) was refluxed in dioxane (30 mL) for 3 hr. Excess of solvent was removed and the residue poured into cold water and neutralised with sodium bicarbonate. The compound, thus obtained, was filtered, washed, dried and recrystallised from aq. ethanol to obtain **5c**, mp 145 °C, yield 69%; IR(KBr): 3265, 2700, 1700, 1685, 1610, 1590, 1550, 1480 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.6(d, 2H, SCH_2CO), 6.9-7.8(m, 7H, Ar-H), 8.4-8.6(b, 1H, NH).

Following identical procedure **5a**(186 °C, 63%), **5b**(160 °C, 62%), **5d**(125 °C, 62%) and **5e**(162 °C, 65%) were prepared as well as **7c** (192 °C, 67%); IR(KBr): 3260, 2730, 1700, 1680, 1590, 1550, 1485 cm^{-1}; ^{1}H NMR(DMSO-d_6): δ1.9(s, 3H, CH_3) 3.6(d, 2H, SCH_2CO), 4.2(d,2H, OCH_2) 6.8-7.5(m,

7H, Ar H), 8.2-8.3(b, 1H, NH). Likewise **7a** (178 °C, 65%), **7b**(182 °C, 67%), **7d**(162 °C, 73%) and **7e**(185 °C, 79%) were obtained.

3-(2-Tolyl)-1,2,4-triazolo [3,4-*b*]indolo[3,2-*e*]-[1,3,4]thiadiazole 6a. A slurry of 5-(2-tolyl)-3-mercapto-4- [1′*H*-2′(3′*H*)-oxoindol-3′-yl)imino]-1,2,4-triazole **3d**(3.35g, 0.01 mole) in conc. sulphuric acid (2.0 mL) was made below 15 °C and left at room temperature for 2 hr and then poured onto crushed ice. It was neutralised with ammonia solution. The compound obtained was filtered, washed, dried and recrystallised from aq. ethanol to get **6a**, mp 136 °C, yield 65%; IR(KBr): 1610, 1550, 1490, 1470 cm^{-1}; ^1H NMR(DMSO-d_6): δ 2.1(s, 3H, CH_3), 7.2-7.9(m, 8H, Ar-H).

Similarly, **8a** [mp 189 °C, yield 67%; IR (KBr): 2810, 1610, 1550, 1490, 1470 cm^{-1}; ^1H NMR(DMSO-d_6): δ 4.5(d, 2H, OCH_2) 6.9-7.5(m,9H,Ar-H)], **6b**(124 °C, 60%), **6c**(255 °C, 58%), **6d**(165 °C, 65%), **8b**(122 °C, 68%), **8c**(132 °C, 56%) and **8d**(245 °C, 65%) were prepared.

All the compounds (**3** to **8**) reported gave satisfactory elemental analyses (Carbon: ±0.3%; Hydrogen: ±0.4% and Nitrogen: ±0.4%).

References

1 Katritzky A R & Rees C W, *Comprehensive heterocyclic chemistry,* Vol 1, 1st Edn (Pergamon Press), **1984**, p 159.
2 Kornet M J & Thio A P, *J Med Chem,* 19, **1976**, 892.
3 Hoechst A G, *Japan Kokai* 78135578 , **1978**; *Chem Abstr,* 90, **1979,** 137699n.
4 Peterson W C, *US Pat* 4683000, (**1987**); *Chem Abst*, 107, **1987**, 217644a.
5 Baasnes B, Schwamborn M, Santel H & Joachim L K, *Eur Pat Appl EP* 422470; *Chem Abstr*, 115, **1991**, 71589c.
6 Singh S P, Parmar S S, Raman K & Stenberg I, *Chem Rev,* 81, **1981**, 175.
7 Naik H, Naik S K, Meher S S & Nayak A, *J Indian Chem Soc,* 60, **1983**, 674.
8 Giri S & Khan M H, *Asian J Chem,* 4, **1992**, 812.
9 Meiser W, Buechel K H, Kramer W & Grewe F, *Ger Pat* 2207576, **1973**; *Chem Abstr,* 79, **1973,** 105257.
10 Shida T, Watanabe T, Yamazaki S, Shinkawa H & Satake K, *Eur Pat Appl EP* 189300, **1986**; *Chem Abstr*, 105, **1986**, 172480j.
11 Euchi O & Toshiji E. *Jpn Kokari JP* 0504976, **1992**; *Chem Abstr*, 119, **1993**, 8813.
12 Katritzky A R & Rees C W, *Comprehensive heterocyclic chemistry,* Vol 1, Ist Edn (Pergamon Press) **1984**, p 198, 398.
13 Thibault T D, *US Pat* 4436549, **1984**; *Chem Abstr*, 101, **1984**, 23510j.
14 Singh J S, Khan M H, Tewari N & Nizamuddin, *Indian J Chem*, 33B, **1994**, 350.
15 Tewari S, Tewari N, Agrawal T, Khan M H & Nizamuddin, *Indian J Chem*, 34B, **1995,** 1010.
16 Agrawal T, Tewari N, Khan M H & Nizamuddin, *Indian J Chem,* 33B, **1994**, 603.
17 Singh K, Tewari N & Nizamuddin, *Indian J Chem,* 32B, **1993**, 1086.
18 Bose A K, Garratt S & Pelosi J J, *J Org Chem,* 28, **1963**, 730; *Chem Abstr*, 58, **1963**, 9071d.
19 Reid J R & Heindel N D, *J Heterocyclic Chem,* 13, **1976**, 925.